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(54) Title: BIOLOGICALLY ACTIVE COMPOSITION

(57) Abstract

A biologically active stick composition comprising a biologically active agent dissolved in a carrier system including an unsaturated fatty acid alcohol in mutual dissolution with an alkylene glycol as a solvent for said biologically active agent and a stiffening agent therefor, said stiffening agent imparting stick consistency to the composition, said alkylene glycol preferably being present in an amount of more than 12%. The composition can be prepared by dissolving the active agent in the solvent, combining the solution with the stiffening agent and shaping the formulation into a stick. The composition is especially intended for use as a medicament, preferably in the treatment of dermatological conditions, where it has been found to possess outstanding bioavailability properties.

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BIOLOGICALLY ACTIVE COMPOSITION

TECHNICAL FIELD

The present invention relates to the field of biologically active compositions and, in particular, to a biologically active stick composition. Preferably the invention relates to pharmaceutical compositions but, other applications outside the medical field are possible within the scope of the invention.

The invention also relates to the use of such compositions as medicaments and for the manufacture of stick medicaments for treating dermal conditions, as well as to a process for the preparation of such compositions.

BACKGROUND OF THE INVENTION

One of the problems associated with topical medical treatment with high potency drugs is in the application of the composition. Most compositions intended for dermatological treatment of the skin are based on cream, ointment of gel vehicles and, when these are applied to the skin, the incidence of extralesional treatment can be substantial; areas surrounding the lesion to be treated as well as the fingers used to apply a product can be affected by the drug.

By using stick compositions having higher viscosities, which can be housed within a protective package, such extralesional treatment can be avoided or at least substantially eliminated. Another advantage of stick formulations is that, by their use, it is simple to achieve a uniform distribution of drug over the lesion to be treated.

Stick based products are not novel in the treatment of skin conditions and several active compounds have been formulated into sticks. Stick compositions, as herein referred to, are formed from erodible, usually soft and waxy materials having a solid consistency. When rubbed across the skin, such compositions are eroded and deposit a coating of their constituent material on the skin. Ge-

nerally, stick compositions include mixtures of lipids and surfactants as carriers.

A major drawback of those stick compositions used today, however, results from the fact that many drugs, at best, are only marginally soluble in their lipid based formulations and, therefore, must be incorporated into stick compositions as suspended solid particles. This, however, leads to several disadvantages, the most serious one being sedimentation of the active ingredient during manufacture. The method used to manufacture stick compositions involves heating, mixing, packing and cooling and, during the heating, mixing and cooling steps, the viscosity of the lipid mixture can be sufficiently low to allow the suspended active drug to settle. The resulting sedimentation of the active ingredient reduces the homogeneity of the composition and can prevent the product from meeting the standards required for pharmaceutical products.

Several solutions to the sedimentation problem have been proposed. Some are based on mechanical measures, which involve regularly turning any vessel used to accomodate the composition before it has set, so that the drug particles are maintained in a suspended state. Others involve the addition of thickening agents to form thixotropic gels. None of these proposals, however, have enabled the manufacture of homogeneous formulations in a reproducible way.

Another disadvantage with topical formulations in general, and stick formulations in particular, is the poor bioavailability of the active drug to the skin. For topical dermatological formulations containing corticosteroides, bioavailability can be in the order of a few percent. Low bioavailability has many implications. One is that the effect of a drug can be variable and non-reproducible, both at the site of application and systemically. Another is that, when conditions at the site of

application are favourable for the penetration of a drug, systemic concentrations thereof can reach toxic levels.

A corticosteroid stick product containing propylene glycol or 1,3-butylene glycol is previously known from US 4,299,828. However, said product is not based on the use of an unsaturated fatty acid alcohol as a solvent and the alkylene glycols referred to are not utilized as solvents but rather as anti-microbial compounds. Furthermore, it is specifically stated that said anti-microbial compound is not dissolved in the stick but dispersed therein (col 3 lines 35-40 and claim 1), i.e. the stick is not a homogeneous product. In addition thereto the preferred percentage of the alkylene glycol is disclosed as 2-10 and optionally 3-8 % by weight (col 3 lines 20-22 and claim 1). Thus, the purpose of the alkylene glycol is completely different from that of the present invention where higher percentages of alkylene glycol have been found to give other effects than those referred to in US 4,299,828.

DESCRIPTION OF THE INVENTION

The present invention relates to a completely novel solid composition, especially a stick composition, for biologically active agents, which may seem similar to the aforementioned lipid based stick products, but which is of a completely different structure and thereby possessed of completely different properties as compared thereto.

More specifically, the solid compositions according to the present invention do not rely upon mechanical means to ensure uniform distribution of the biologically active agent. The active agent is distributed in a lipid carrier, but not in a suspended or dispersed state as previously practised but, rather, in a dissolved state. Thus, it has unexpectedly been found that, in spite of the generally poor solubility of the biologically active compounds previously formulated in stick compositions, a more or less complete dissolution of the biologically ac-

tive agent can be obtained by means of the present invention into a completely homogeneous solid composition.

A first object of the invention is to provide a composition which contains a biologically active agent in a dissolved state.

Another object of the invention is to provide a composition which possesses an enhanced stability against sedimentation of the active agent.

Still another object of the invention is to provide homogeneous compositions.

One other object of the invention is to provide compositions possessing an enhanced release rate for the active agent, i.e. improved bioavailability, especially for use in dermatology.

Still another object of the invention is to provide compositions, the consistency of which can be controlled by means of the composition thereof, especially to accomplish a composition to be administered via the skin.

One other object of the invention is to provide a composition for use as a drug or medicament, especially for the treatment of dermatological conditions.

Still another object of the invention is to provide a process for the preparation of compositions, especially stick compositions of the type referred to above.

Still other objects of the invention should be obvious to a person skilled in the art after having studied the following description of the invention.

Thus, according to a first aspect of the present invention there is provided a solid composition comprising a biologically active agent dissolved in a carrier system, wherein the carrier system includes a specific combination of solvents for the active agent and a stiffening agent for imparting a solid consistency to the composition. Preferably, the stiffening agent is a viscosity enhancing agent capable of imparting a soft and erodible consistency to the composition.

It is preferred that compositions in accordance with

the present invention are stick compositions as hereinbefore defined.

More specifically a solid composition is claimed, wherein the carrier system includes an unsaturated fatty acid alcohol in combination with an alkylene glycol selected from propylene glycol, butylene glycol, dipropylene glycol and/or dibutylene glycol as a solvent for the active agent and a stiffening agent for imparting a solid consistency to the composition, said alkylene glycol being present in an amount that gives mutual dissolution with said unsaturated fatty acid alcohol as well as dissolution of said active agent.

By employing the present invention, it is possible to combine the good characteristics of a homogeneous solution with the good characteristics of a stick products, which combination has hitherto not been possible.

As the carrier system preferably comprises miscible solvent and viscosity enhancing substances, compositions in accordance with the invention can form stable stick compositions without any substantial sedimentation of the biologically active agent.

Furthermore, the solvent combination used should be capable of dissolving the biologically active agent at a temperature where significant decomposition of said agent is avoided.

Generally, the biologically active agent is any biologically active compound, or mixture of compounds, which can be dissolved to a substantial extent in the carrier system of the present invention. Typically, this means that the biologically active agent is a lipophilic, i.e. lipid soluble, compound. In this context the invention is of special interest in connection with drugs or medical compounds but, of course, the inventive idea is applicable to any biologically active agent for which a stick formulation is appropriate. The term "biologically active agent" should be interpreted in a broad, conventional

sense to mean an element, compound or composition which, when present in an effective amount, will interact with living organisms, preferably to elicit a therapeutic effect.

There are a large number of agents falling within the avove-mentioned definitions and which can be formulated in compositions according to the invention. However, some specific examples include steroids, e.g. corticosteroids, vitamins, sex hormones, biologically active lipids, fatty acids, antibiotics or antimicrobials and local anestetics. In this connection it should be noted that, as is common in the art, the compounds can be used per se or in the form of salts or esters or other chemically modified forms thereof.

Some examples within the above-mentioned groups include vitamins A, D2, D3, E, K and derivatives thereof, androgens, estrogens and derivatives thereof, amide type local anestetics and antimicrobials such as antivirals, antibacterials, antiprotozoals and antifungals. Further examples include fluocinonide, omega-3-fatty acid and azelaic acid, and salts and esters thereof, clobetasol, and salts and esters thereof, and betamethasone and salts and esters thereof, particularly betamethasone-17-valerate and betamethasonedipropionate.

Generally the solvent used is capable of dissolving the specific active agent used to the desired extent. Preferably the solvent comprises an unsaturated C_{16}-C_{20}-fatty acid alchol, more preferably C_{18}-fatty acid alcohol, in mutual dissolution with the alkylene alcohol referred to. In the case of said unsaturated C_{18}-fatty acid alcohol, it is preferably selected from oleyl alcohol, ricinolyl alcohol, linolyl alcohol and/or linolenyl alcohol and more preferably is oleyl alcohol. Another example of a C_{18}-fatty acid alcohol is eleosteryl alcohol, while a preferable example of a C_{16}-fatty acid alcohol is palmitoleyl alcohol, and a preferable example of a C_{20}-fatty acid alcohol is arachidonyl alcohol.

In more general terms the unsaturated fatty acid alcohol is used in combination with an alkylene glycol having the general formula $R(OH)_2$; a di- or poly-alkylene glycol having the general formula $HOR(OR)_nOROH$; a C_4-C_{36} (e.g. C_4-C_{18}) aliphatic primary alcohol; or a mixture of two or more such compounds. In the foregoing formulae, each group R can be the same or different and is an alkyl, preferably a C_2-C_6 alkyl group and $n \geq 0$. Preferred groups R are ethyl, propyl and butyl groups and the preferred glycols thus include propylene glycol, butylene glycol, dipropylene glycol and dibutylene glycol.

In addition to the above-mentioned unsaturated fatty acid alcohols other primary alcohols can be included in the composition, such as lauryl alcohol, myristyl alcohol, palmityl alcohol and/or stearyl alcohol.

In one preferable embodiment of the invention an additional solvent can be included wich is selected from lipid esters, such as fatty acid esters and esters of sorbic acid. Examples of fatty acids from which such esters can be derived include lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, ricinoleic acid, linolic acid and linolenic acid. The precursor alcohols are preferably the C_1-C_6-alkanols methanol, etanol, propanol, butanol, pentanol and hexanol with either straight or branched carbon chains. Especially preferred esters in this respect are the propyl esters, including the isopropyl esters, especially isopropylpalmitate.

Still further additional solvents usable in the invention are the C_2-C_6 alkylene carbonates, e.g. ethylene, propylene or butylene carbonate, preferably propylene carbonate.

The viscosity enhancing agent should be chosen such that it is compatible with the solvent and so that it imparts the desired viscosity or consistency thereto. Generally this means that said viscosity enhancing agent is a waxy substance.

In preferred embodiments of the invention said waxy substance is a natural or synthetic wax which is generally defined as monoester of a long-chained (typically C_{14}-C_{36}, e.g. C_{18}-C_{24}) carboxylic acid with a long-chained (typically C_{16}-C_{36}) alcohol. In both cases the carbon chains, preferably, are unbranched aliphatic chains.

In another embodiment the waxy substance is a fat and, preferably, a triglyceride of a C_{18}-C_{36} fatty acid or a glycol (typically an alkylene glycol as herein before defined and comprising 2-6 carbon atoms) ester of a C_{18}-C_{36} fatty acid.

Combinations of said waxes and/or waxy substances may be employed and, in an especially preferred embodiment of the invention, the viscosity enhancing agent comprises a combination of a natural and/or synthetic wax plus a triglyceride and/or a glycol ester, as defined above, and enables the carrier system's rheological properties to be accurately tailored, for example, to achieve a broad softening point.

Other preferred waxes are paraffin wax and cerasine wax.

In some cases, the viscosity enhancing agent, or waxy substance, can cause the composition to be too viscous. In accordance with the present invention this can be avoided by incorporating into the carrier system an oil having the capacity to plasticize the viscosity enhancing agent and reduce the viscosity of the carrier system to a level that is suitable for the composition's intended purpose. Preferred plasticizing oils include low molecular weight aliphatic acids and alcohols, especially with branched chains, e.g. fluid lanoline.

When the inventive composition is for use as a medicament, it should hardly need mentioning that all of the above-identified ingredients, as well as other optional conventional further ingredients, should be pharmaceutically acceptable and non-toxic when the composition is used in the intended manner.

The combination of solvent and viscosity enhancing agent in the carrier system should be selected in line with the principles given above such that a proper dissolution rate, consistency and release rate are obtained. Generally this means that the amounts of the different ingredients could be decided experimentally using techniques well known to persons skilled in the art. However, in general the amount of solvent can be within the range of 20-85 % by weight, the amount of viscosity enhancing agent can be within the range of 15-80 % by weight and the amount of plasticizing oil can be within the range of 0- 30 % by weight, based on the total weight of the carrier system.

Preferably the amount of solvent is within the range of 25-75, more preferably 40-60, percent by weight, while the amount of viscosity enhancing agent is within the range of 15-55, more preferably 25-50, percent by weight and the amount of plasticizing oil is within the range of 0-30, more preferably 2-20, percent by weight.

As was mentioned above it has been found possible to combine the unsaturated fatty acid alcohol with the alkylene glycol in such properties that mutual dissolution of the solvents as well as full dissolution of the active agent in the composition is accomplished. Generally this means that the amount of alkylene glycol is more than 12 % by weight and preferably at least 15 % by weight, based on the total weight of the carrier system.

According to an especially preferable embodiment of the invention the amount of the alkylene glycol solvent, preferably propylene glycol, is within the range of 12-23, preferably 15-23, % by weight, based on the total weight of the carrier system, more preferably 12-20, especially 15-20, % by weight.

In another preferable embodiment of the invention, where said additional solvent is present, the weight ratio of oleyl alcohol : additional solvent is within the

range of 1:2 to 5:1, preferably 1:2 to 3:1 and more preferably 1:2 to 2:1.

The amount of the biologically active agent is of course dependent on the effect to be accomplished. Generally, however, the upper limit will be the active agent's solubility limit in the carrier system, which can be up to 40 percent by weight or in some cases merely up to 10 or even 5 percent by weight, in all cases calculated on the weight of the carrier system. Preferably the range thereof can be 0.01 - 10, especially 0.02 - 5, percent by weight, on the same basis. The exact amount, however, is easily determined by a person skilled in the art with reference to the optimum or maximum effect it is wished to obtain.

It is especially preferred that compositions according to the invention are for pharmaceutical or medical purposes. In this case, the biologically active agent can be a therapeutic or prophylactic agent of any kind. The other ingredients employed must be selected in accordance with the general principles applying to the formulation of medical or pharmaceutical compositions.

In an especially preferred embodiment, the inventive composition comprises a medicament for administration to the skin, or for dermal administration. In such a case a person skilled in the art will formulate the composition such that its viscosity will be proper for administration in that way and such that the release of the active compound will have the desired profile.

Thus, from the above-mentioned it should be clear that stick compositions according to the present invention are especially well suited for the treatment of dermatological conditions.

According to yet another aspect of the invention there is also provided a process for the preparation of compositions, preferably stick compositions, in accordance with the invention. Said process comprises dissolving the biologically active agent in the solvent there-

for, combining the resulting solution with a viscosity enhancing agent so as to impart a solid consistency to said solution and shaping the resulting formulation into a stick.

Preferably the active agent is dissolved in the solvent, or part thereof, and the solution obtained is then added to a melted mass of the viscosity enhancing agent, preferably while being stirred. When a homogeneous mass has been obtained, said mass, preferably after some cooling, can then be poured into a mould and allowed to cool and set in the desired shape. Proper temperatures in this respect are easily determined by a person skilled in the art.

The composition is physically stable below +50°C although softening of the structure may occur. The composition should be capable of returning to its original viscosity after cooling to +30°C or lower. This may also be valid after heating to temperatures in excess of +50°C.

After such heating followed by cooling to +30°C or lower the composition will still be homogeneous. This is an advantage compared to such stick formulations where the active drug is in solid form, i.e. suspended. In these compositions the active drug will settle out at higher temperatures and form an unhomogeneous preparation.

EXAMPLES

The invention will now be exemplified further by means of the following non-limiting working examples.

EXAMPLE 1

Stick compositions 1-10 were prepared from the following ingredients, the figures being percentages by weight.

	1	2	3	4	5	6	7	8	9	10
Fluid lanoline	14.3	14.3	12.9	12.9	15.4	16.7	17.6	17.6	18.5	11.9
Paraffin wax	7.1	7.1	6.4	6.4	5.4	3.5	3.7	3.7	-	5.8
Ceresine wax	5.4	5.4	4.9	4.9	5.8	4.7	4.9	4.9	3.9	4.5
Syncrowax ERLC	14.3	14.3	12.9	12.9	8.6	7	-	-	-	11.9
Syncrowax HGLC	10.7	10.7	9.6	9.6	12.9	11.7	14.7	14.7	15.5	8.9
Oleyl alcohol	35.6	35.6	32	32	38.4	41.7	43.7	43.7	46	29.7
Isopropylpalmitate	12.5	12.5	11.2	11.2	13.5	14.6	15.4	15.4	16.1	10.4
Propylene glycol	-	-	10	10	-	-	-	-	-	16.7
Clobetasol propionate	0.05	-	-	-	-	-	-	-	-	-
Betamethasone-valerate	-	0.12	-	-	-	-	-	-	-	-
Fluocinonide	-	-	0.05	-	-	-	-	-	-	-
Betamethasone-dipropionate	-	-	-	-	0.067	0.067	0.067	-	0.067	0.067

The manufacturing process was as follows:

The active agent was dissolved in the oleyl alcohol. Separately the lanoline, paraffin wax, ceresine wax, glycol esters, triglycerides and the isopropyl palmitate were mixed together in a glass beaker.

The mixture in the glass beaker was then heated to about 75°C and was allowed to melt while being stirred. The oleyl alcohol and active agent solution, also heated to +75°C, was then added thereto and the combination was stirred for 10 minutes.

After reducing the temperature to about 65°C the resulting composition was poured into a stick mould and allowed to cool and solidify.

These compositions were then tested by means of conventional blanching tests (blanching is an established method of assaying biological activities of steroid preparations) and compared with commercial creams and ointments. The results of said tests are summarized as follows:

Product	Test mean value
Comp. 1	1.78
2	1.25
3	1.81
4	-
5	1.69
6	1.67
7	1.33
8	0.03
9	1.47
10	2.53
Lidex Ointment x)	2.42
Temovate Ointment xx)	2.75
Betamethasone valerate Ointment (Fougera) xxx)	1.94
Diprolene Cream	2.64
Diprolene Ointment	2.72

x) 0,05% fluocinonide
xx) 0,05% clobetasol propionate
xxx) 0,12% betamethasone valerate

From said results it can be seen that composition No. 10 according to the invention was bioequivalent to all commercial cream and ointment products, which is indeed unexpected and means a great contribution to the art now that a stick product can compete with well-estab-

lished creams and ointments. Furthermore, it should be borne in mind that the new stick claimed possesses great advantages also compared to known stick products as has been described above (completely homogeneous product with no sedimentation problems, etc.).

CLAIMS

1. A solid composition comprising a biologically active agent dissolved in a carrier system, wherein the carrier system includes an unsaturated fatty acid alcohol in combination with an alkylene glycol selected from propylene glycol, butylene glycol, dipropylene glycol and/or dibutylene glycol as a solvent for the active agent and a stiffening agent for imparting a solid consistency to the composition, said alkylene glycol being present in an amount that gives mutual dissolution with said unsaturated fatty acid alcohol as well as dissolution of said active agent.

2. A compostion as claimed in claim 1, wherein the amount of said alkylene glycol is more than 12 % by weight, based on the total weight of the carrier system.

3. A compostion as claimed in claim 2, wherein the amount of said alkylene glycol is at least 15 % by weight.

4. A composition as claimed in any one of the preceding claims, wherein said unsaturated fatty acid alcohol is an unsaturated C_{16}-C_{20}-fatty acid alchol, preferably an unsaturated C_{18}-fatty acid alchol.

5. A composition as claimed in claim 4, wherein said unsaturated C_{18}-fatty acid alcohol is selected from oleyl alcohol, ricinolyl alcohol, linolyl alcohol and/or linolenyl alcohol, preferably oleyl alcohol.

6. A composition as claimed in any one of the preceding claims, wherein the stiffening agent is a viscosity enhancing agent capable of imparting a soft and erodible consistency to the composition.

7. A composition as claimed in any one of the preceding claims, wherein the biologically active agent is a lipophilic compound, preferably a lipophilic drug.

8. A composition as claimed in claim 7, wherein the biologically active compound is selected from steroids, including corticosteroids, sex hormones, including andro-

gens and estrogens and derivatives thereof, vitamins, including vitamins A, D2, D3, E, K and derivatives thereof, biologically active lipids, fatty acids, antibiotics and antimicrobials, including antivirals, antibacterials, antiprotozoals and antifungals, and local anestetics, preferably of the amide type.

9. A composition as claimed in claim 8, wherein the biologically active compound is selected from fluocinonide, omega-3-fatty acid and azelaic acid and salts and eters thereof.

10. A composition as claimed in claim 8, wherein the biologically active compound is clobetasol or a salt or an ether thereof, preferably clobetasol propionate.

11. A composition as claimed in any one of the preceding claims, wherein the alkylene glycol is propylene glycol.

12. A composition as claimed in any one of the preceding claims, wherein the solvent additionally comprises a C_1-C_6-alkanol ester of a fatty acid and/or a C_1-C_6-alkanol ester of sorbic acid.

13. A composition as claimed in claim 12, wherein said additional solvent comprises propyl (incl. isopropyl) myristate, palmitate, oleate, stearate and/or laurate, and/or the propyl (incl. isopropyl) ester of sorbic acid.

14. A composition as claimed in claim 13, wherein said additional solvent is isopropylpalmitate.

15. A composition as claimed in any one of the preceding claims, wherein the viscosity enhancing agent is a waxy substance.

16. A composition as claimed in claim 15, wherein the waxy substance comprises a natural and/or synthetic wax, preferably a monoester of a long-chained carboxylic acid with a long-chained alcohol; a fat, preferably a triglyceride of a C_{18}-C_{36} fatty acid; a glycol ester of a C_{18}-C_{36} fatty acid; or a mixture of two or more such compounds.

17. A composition as claimed in claim 16, wherein the waxy substance comprises a combination of a natural or synthetic wax and a triglyceride and/or a glycol ester.

18. A composition as claimed in any one of the preceding claims, wherein the carrier system also comprises an oil capable of plasticizing the viscosity enhancing agent and reducing the viscosity of the carrier system.

19. A composition as claimed in claim 18, wherein the plasticizing oil is selected from low molecular weight aliphatic acids and alcohols, preferably having branched chains, and preferably is fluid lanoline.

20. A composition as claimed in any one of the preceding claims, wherein the amount of solvent is within the range of 20-85 % by weight, the amount of viscosity enhancing agent is within the range of 15-80 % by weight and the amount of plasticizing oil is within the range of 0-30 % by weight, based on the total weight of the carrier system.

21. A composition as claimed in claim 20, wherein the amount of solvent is within the range of 25-75, preferably 40-60, % by weight, the amount of viscosity enhancing agent is within the range of 15-55, preferably 25-50, % by weight and the amount of plasticizing oil is within the range of 0-30, preferably 2-20, % by weight.

22. A composition as claimed in any one of the preceding claims, wherein the amount of said alkylene glycol is within the range of 12-23, preferably 15-23, % by weight, more preferably 12-20, especially 15-20, % by weight.

23. A composition as claimed in any one of claims 12-22, wherein the weight ratio of unsaturated fatty acid alcohol : additional solvent is within the range of 1:2 to 5:1, preferably 1:2 to 3:1, especially 1:2 to 2:1.

24. A composition as claimed in any one of the preceding claims, wherein the biologically active agent is

present in a concentration of up to the solubility limit thereof in the carrier system.

25. A composition as claimed in any one of the preceding claims, wherein the concentration of the biologically active agent is 0,01-10, preferably 0,02-5, % by weight, based on the weight of the carrier system.

26. A composition as claimed in any of the preceding claims, wherein said composition is a stick composition.

27. A composition as claimed in any one of the preceding claims for use as a medicament, said biologically active agent being a therapeutically or prophylactically active agent.

28. A composition as claimed in claim 27, for topical application to the skin of a mammal, especially man, wherein the composition has a viscosity that is adapted for such application.

29. A composition as claimed in any of the preceding claims, wherein the biologically active compound is betamethasone, or a salt or ester thereof, preferably betamethasone-17-valerate or betamethasonedipropionate.

30. Use of a composition as claimed in any of the preceding claims for the preparation of a medicament for therapeutic or prophylactic treatment of a dermatological condition.

31. A use as claimed in claim 30, wherein the composition is as claimed in any one of claims 2-29.

32. A process for the preparation of a biologically active composition as claimed in any of claims 1-29, comprising dissolving the biologically active agent in said solvent therefor, combining the resulting solution with a viscosity enhancing agent so as to impart a solid consistency to said solution and shaping the resulting composition into a desired form.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 97/00721

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/06, A61K 31/58, A61K 31/575, A61K 31/20
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EMBASE, MEDLINE, WPI, US PAT FULLTEXT, CAPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4299828 A (YU-CHANG J WANG ET AL), 10 November 1981 (10.11.81), column 1, line 65 - column 2, line 3; column 2, line 28 - line 34; column 2, line 65 - column 3, line 12 --	1-32
A	US 5174995 A (ADRIAN F. DAVIS), 29 December 1992 (29.12.92) --	1-32
A	US 4711906 A (OTTO VON STETTEN ET AL), 8 December 1987 (08.12.87) -- --------	1-32

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
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Date of the actual completion of the international search	Date of mailing of the international search report
1 August 1997	08 -08- 1997
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anneli Jönsson Telephone No. +46 8 782 25 00

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 97/00721

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4299828 A	10/11/81	AU 5794680 A	04/12/80
		BE 883573 A	01/12/80
		CA 1155394 A	18/10/83
		DE 3020616 A,C	04/12/80
		FR 2457687 A,B	26/12/80
		GB 2050831 A,B	14/01/81
		JP 1691407 C	27/08/92
		JP 3053286 B	14/08/91
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		EP 0271332 A,B	15/06/88
		SE 0271332 T3	
US 4711906 A	08/12/87	DE 3446873 A,C	10/07/86
		EP 0185374 A,B	25/06/86
		SE 0185374 T3	

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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A61K 9/06, 31/58, 31/575, 31/20

A1

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(71) Applicant *(for all designated States except US)*: BIOGLAN AB [SE/SE]; P.O. Box 50310, S-202 13 Malmö (SE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: LINDAHL, Åke [SE/SE]; Ringduvevägen 50, S-274 33 Skurup (SE). BRYLAND, Rickard [SE/SE]; Västra Rönneholmsvägen 60B, S-217 41 Malmö (SE).

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(81) Designated States: AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), EE, EE (Utility model), ES, FI, FI (Utility model), GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: BIOLOGICALLY ACTIVE COMPOSITION

(57) Abstract

A biologically active stick composition comprising a biologically active agent dissolved in a carrier system including an unsaturated fatty acid alcohol in mutual dissolution with an alkylene glycol as a solvent for said biologically active agent and a stiffening agent therefor, said stiffening agent imparting stick consistency to the composition, said alkylene glycol preferably being present in an amount of more than 12%. The composition can be prepared by dissolving the active agent in the solvent, combining the solution with the stiffening agent and shaping the formulation into a stick. The composition is especially intended for use as a medicament, preferably in the treatment of dermatological conditions, where it has been found to possess outstanding bioavailability properties.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 97/00721

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/06, A61K 31/58, A61K 31/575, A61K 31/20
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 August 1997	08 -08- 1997
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anneli Jönsson Telephone No. +46 8 782 25 00

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 97/00721

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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US 4711906 A	08/12/87	DE 3446873 A,C	10/07/86
		EP 0185374 A,B	25/06/86
		SE 0185374 T3	

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Awapatent AB
P.O. Box 45086
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PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	02-07-1998
Applicant's or agent's file reference: 2978301	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE97/00721	29-04-1997	30-04-1996

Applicant
Bioglan AB
et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in som Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary axamination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/ Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. 08-667 72 88 Telex 17978 PATOREG-S	Authorized officer Telephone No. 08-782 25 00

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 2978301	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/SE97/00721	International filing date *(day/month/year)* 29.04.1997	Priority date *(day/month/year)* 30.04.1996
International Patent Classification (IPC) or national classification and IPC6 A 61 K 9/06, A 61 K 31/58, A 61 K 31/575, A 61 K 31/20		
Applicant Bioglan AB et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report

   II ☐ Priority

   III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

   IV ☐ Lack of unity of invention

   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI ☐ Certain documents cited

   VII ☐ Certain defects in the international application

   VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18.11.1997	18.06.1998
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Telex 17978 PATOREG-S Facsimile No. 08-667 72 88	Authorized officer Anneli Jönsson Telephone No. 08-782 25 00

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE97/00721

I Basis of the report

1. This report has been drawn on the basis of *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

☒ the international application as originally filed.

☐ the description, pages _____, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____.

☐ the claims, Nos. _____, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. _____, filed with the letter of _____,
Nos. _____, filed with the letter of _____.

☐ the drawings, ~~sheets~~/fig _____, as originally filed,
~~sheets~~/fig _____, filed with the demand
~~sheets~~/fig _____, filed with the letter of _____,
~~sheets~~/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, ~~sheets~~/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE97/00721

V. Resoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-32	YES
	Claims		NO
Inventive step (IS)	Claims	1-32	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-32	YES
	Claims		NO

2. Citations and explanations

The claimed invention relates to a biologically active stick composition. The active agent is dissolved in a carrier system which includes an unsaturated fatty acid alcohol in combination with an alkylene glycol, which is a solvent for the active agent, and a stiffening agent. The use of the composition for preparation of a medicament for therapeutic or prophylactic treatment and a process for the preparation of a biologically active composition are also claimed.

The present invention solves the problems with sedimentation of the active ingredient as the active component is dissolved in the composition. Previous compositions contains the active component as suspended solid particles. These compositions have poor bioavailability. In the present invention a dissolution is created of the alkylene glycol, the unsaturated fatty acid alcohol as well as the active agent.

Document US 4 299 828 A discloses a composition in the form of a lipophilic stick. The composition comprises corticosteroids and propylene glycol or 1,3-butylene glycol in amounts of 3-8% (at least 12% in the present invention). The composition according to the present invention comprises alkylene glycols in an amount that gives a mutual dissolution with said unsaturated fatty acid and the active agent (according to claims 2 and 3 "at least 15% by weight"). However, the composition disclosed in the US 4 299 828 A is not a homogenous composition, it contains dispersed particles of the alkylene glycol. Therefore, the document only discloses the general state of the prior art.

.../...

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V

Document US 5 174 995 A discloses a topical drug release system. The drug is initially saturated in the composition which in situ forms a supersaturated composition on a waterwetted area of the body. Solubilizers are, for example, propylene glycol, 1,3-propylene diol. The composition can also contain a thickening agent and a gelling agent, for instance, natural gums, tragacanth, carrageen. The claimed invention can contain waxy materials as stiffening agents. The document does not disclose a solid composition according to the claimed invention. Therefore, this document also only discloses the general state of the prior art.

Document US 4 711 906 A discloses a stable liquid diclofenac preparation which comprises dissolvent mixed of propylene glycol and polyethylene glycol and water. A solid, topical composition in the form of the stick claimed is not disclosed. Therefore, the document also only discloses the general state of the prior art.

Consequently, the claimed invention according to claims 1-32 is considered to involve novelty, inventive step and industrial applicability.